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Interventions on Prevention of Postoperative Atrial Fibrillation in Patients Undergoing Heart Surgery

A Meta-Analysis

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Background—Postoperative atrial fibrillation (AF) is a common complication of cardiac surgery and has been associated with increased incidence of other complications and increased hospital length of stay (LOS). Prevention of AF is a reasonable clinical goal, and, consequently, many randomized trials have evaluated the effectiveness of pharmacological and nonpharmacological interventions for prevention of AF. To better understand the role of various prophylactic therapies against postoperative AF, a systematic review of evidence from randomized trials was performed.

Methods and Results—Fifty-two randomized trials (controlled by placebo or routine treatment) of β -blockers, sotalol, amiodarone, or pacing were identified by systematic literature search. The 3 drug treatments each prevented AF with the following odds ratios (ORs): β -blockers, 0.39 (95% CI, 0.28 to 0.52); sotalol, 0.35 (95% CI, 0.26 to 0.49); and amiodarone, 0.48 (95% CI, 0.37 to 0.61). Pacing was also effective; for biatrial pacing, the OR was 0.46 (95% CI, 0.30 to 0.71). The influence of pharmacological interventions on LOS was as follows: -0.66 day (95% CI, 2.04 to 0.72) for β -blockers; -0.40 day (95% CI, 0.87 to 0.08) for sotalol; and -0.91 day (95% CI, 1.59 to -0.23) for amiodarone. The influence for biatrial pacing was -1.54 day (95% CI, -2.85 to -0.24). The incidence of stroke was 1.2% in all the treatment groups combined and 1.4% in controls (OR, 0.90; 95% CI, 0.46 to 1.74).

Conclusions— β -Blockers, sotalol, and amiodarone all reduce risk of postoperative AF with no marked difference between them. There is evidence that use of these drugs will reduce LOS. Biatrial pacing is a promising new treatment opportunity. There was no evidence that reducing postoperative AF reduces stroke; however, data on stroke are incomplete. (*Circulation*. 2002;106:75-80.)

Key Words: fibrillation ■ cardiopulmonary bypass ■ complications ■ prevention

Postoperative atrial fibrillation (AF) is a common complication of cardiac surgery, occurring in 25% to 40% of patients.¹ Several reports have indicated that the postoperative AF has been associated with increased hospital length of stay (LOS), increased rates of postoperative stroke, and, in consequence, an increased total cost of surgery.¹ Chronic AF is convincingly shown to cause stroke, and, consequently, prevention of postoperative AF could reduce the risk of this major morbid outcome. However, stroke and transient ischemic attack rates after heart surgery are low (<3%),² and as a result it is difficult to demonstrate benefit from AF prevention in a single trial.

Many clinical trials have evaluated the effectiveness of a variety of pharmacological and nonpharmacological interventions to decrease the incidence of AF. However, often these trials were statistically underpowered and, because of this, inconclusive. None of these trials had sufficient power to reliably estimate an effect of these treatments on LOS or on

stroke, which would be expected to be hard to detect. However, given the usual short duration and overall low morbidity associated with postoperative AF itself, the main indication for AF prophylaxis is still the shortening of LOS and possibly reduction in stroke. Therefore, we undertook a systematic review of evidence from randomized controlled trials to estimate the effect of these interventions on the occurrence of AF, LOS, and stroke.

Methods

Literature Search

The search was performed in accordance with the recommendations of the Cochrane collaboration using Cochrane CENTRAL database, Medline, Embase, and Cinhal from earliest achievable date until April 2001. The initial search terms were *atrial fibrillation* and *surgery*. A hand search of references from reports and earlier reviews was also performed. Abstract books and CD-ROMs from several annual scientific meetings (American College of Cardiology, American Heart Association, North American Society of Pacing and

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Electrophysiology, and European Heart Organization) between 1997 and March 2001 were searched for relevant abstracts. No language restrictions were applied.

Inclusion Criteria for Studies

Although a variety of pharmacological agents and other interventions have been tested for the prevention of postoperative AF, this meta-analysis includes only β -blockers, amiodarone, and pacing, which are the interventions tested in >3 randomized controlled trials. A prior meta-analysis included both digoxin and verapamil,^{3,4} and there have not been any significant recent trials. Therefore, these 2 agents were not included in this analysis.

Because the antiarrhythmic activity and side-effect profile of sotalol differs from that of other β -blockers, sotalol trials were analyzed separately from other β -blockers trials. Studies were only included if they met all of the following criteria: (1) randomized control trials versus placebo or usual care; (2) primary prevention of postoperative AF in postcoronary artery bypass graft surgery or combined coronary graft and valvular surgery; (3) treatment started immediately before the operation, during the operation, or within postoperative intensive care unit (ICU) stay; (4) well-described protocol of intervention; and (5) adequate data on treatment efficacy (supraventricular arrhythmia incidence).

Double-blind and nonblinded studies were included. The primary outcome measure was incidence of postoperative AF or atrial flutter, except where total incidence of supraventricular arrhythmia was documented.

Two other outcome measures, LOS and incidence of stroke, were also analyzed when they could be obtained either from the publication or by direct communication with the authors (authors of studies published during last decade were approached). Four other trials⁵⁻⁸ that directly compared β -blockers and sotalol were identified and analyzed separately.

Three reviewers (E.C., K.S., T.J.G.) independently extracted the data from published sources on the number of patients included, type and route of intervention, incidence of AF or supraventricular tachyarrhythmia, LOS, and stroke. The attempt to contact corresponding authors was made when key information was not available from the index publication. Mailing and e-mail addresses provided by publishers were used. We attempted to obtain missing information on LOS or in-hospital stroke from 23 authors of trials published since 1991. We received 9 responses, including missing information about LOS for 1 study and missing information about stroke for 3 studies.

Statistics

The occurrence rates of AF and stroke were treated as dichotomous variables, and LOS was treated as a continuous variable. For the comparison of the LOS, the weighted mean difference was calculated as a difference between mean values of LOS in treatment and control groups.

Analysis was based on the intention-to-treat principle. Pooled effect estimates and heterogeneity between studies were analyzed by use of REVSTAT 4.1/Metaview 4.1 statistical package with a random effects model.

Results

Pharmacological Interventions

There were 42 trials that evaluated pharmacological prevention of postoperative AF by β -blockers, sotalol, or amiodarone^{6,9-50} published before April 1, 2001. Patient enrollment ranged between 36 and 1000 patients.^{13,24} All studies included patients undergoing coronary artery bypass surgery, and 3 trials also included patients who underwent valvular surgery.^{9,13,39} In all trials most patients were male. Most of the trials excluded patients with severely decreased left ventricular function, and the reported values of mean ejection fraction of the patients enrolled were in the range of 43% to

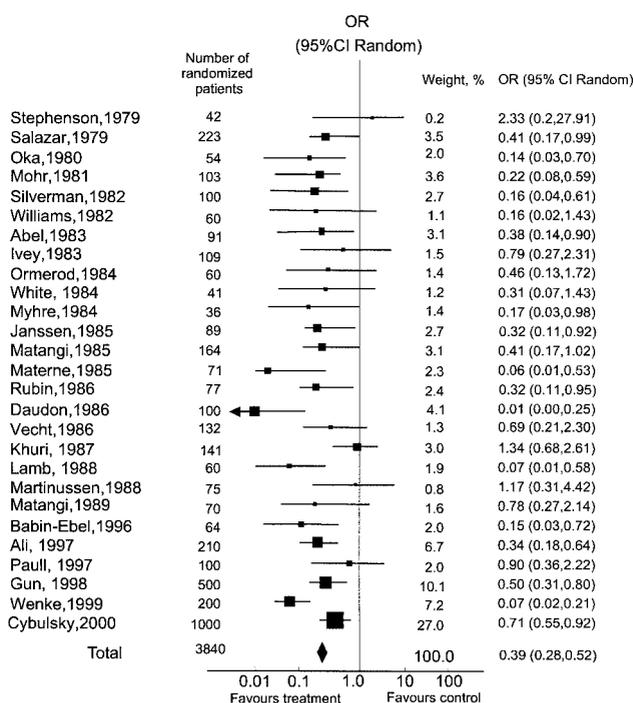


Figure 1. β -Blockers versus placebo or no treatment for the prevention of AF. Test for heterogeneity $P=0.00001$. Test for overall effect $P<0.00001$.

68%.^{19,46} The percentage of patients with history of previous myocardial infarction varied from 26% to 85%.^{25,47} The prevalence of use of preoperative β -blockers varied, because some trials were designed to evaluate the role of β -blocker withdrawal phenomena,²³ whereas others excluded patients not taking β -blockers preoperatively.^{11,24,25} In trials published after 1995, the proportion of patients undergoing β -blocker therapy preoperatively was 61% to 80%.^{12,13,33} The timing of initiation of study treatment varied between the trials, starting before,^{9,10,18,19,25,38,39,41,43,45,48,49} during,⁴⁴ or after^{6,11-17,20-24,26} surgery. In 2 trials,^{16,31} the intervention drug was administered at the end of ICU stay.

All the trials used continuous electrocardiographic (ECG) monitoring or Holter recordings^{6,8,9,21,34,36-39,41,43,48} to detect AF in ICUs. After ICU discharge, daily ECG or predischarge Holter monitoring was used for arrhythmia detection. The follow-up period was usually confined to hospital stay; however, in some trials the monitoring period was extended to 30⁴⁶ and 90 days.^{37,39,41}

Effects on Postoperative AF

There were 27 trials^{6,10-35} that evaluated a β -blocker for prevention of postoperative AF, including 3840 patients. Individual study sample size varied from 41 to 1000 patients. β -Blockers (Figure 1) reduced the percentage of patients with AF from 33% in the control group to 19% in the β -blocker group (OR, 0.39; 95% CI, 0.28 to 0.52), with significant heterogeneity between trials ($P=0.00001$). To assess the reason for this marked heterogeneity, we evaluated the role of specific β -blockers used, the proportion of patients taking β -blockers preoperatively, study size, method of electrocardiographic monitoring, and source where the information for

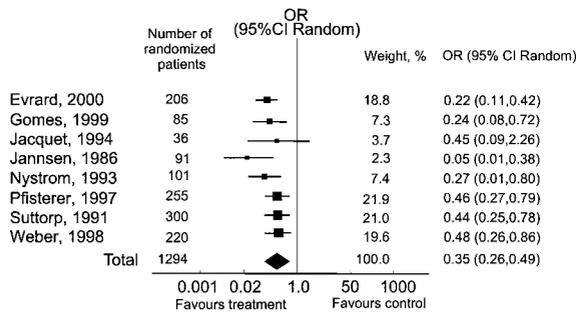


Figure 2. Sotalol versus placebo or no treatment for the prevention of AF. Test for heterogeneity $P=0.25$. Test for overall effect $P<0.00001$.

this meta-analysis was obtained from (studies from peer-reviewed journals versus all others). No reason for heterogeneity between the β -blocker trials was found by these analyses.

There were 8 trials^{6,9,36-41} that evaluated the use of sotalol for prevention of postoperative AF, including 1294 patients (Figure 2). Individual study sample size varied from 36 to 300 patients. Sotalol reduced the percentage of patients with AF from 37% in control group to 17% in a sotalol group (odds ratio, 0.35; 95% CI, 0.26 to 0.49), with no significant heterogeneity between trials ($P=0.25$).

There were 9 trials⁴²⁻⁵⁰ that evaluated the use of amiodarone, including 1384 patients (Figure 3). Individual study size ranged from 77 to 300^{46,47} patients. Amiodarone (Figure 3) reduced the percentage of patients with AF from 37% in the control group to 22.5% in amiodarone group (OR, 0.48; 95% CI, 0.37 to 0.61), with no significant heterogeneity between trials ($P=0.54$).

Sotalol Versus Conventional β -Blockers

Sotalol and other β -blockers were compared directly in 4 trials, including 900 patients.⁵⁻⁸ Sotalol reduced the percentage of patients with AF from 22% in the other β -blocker group to 12% in sotalol group (OR, 0.50; 95% CI, 0.34 to 0.74), with no significant heterogeneity ($P=0.33$).

Pacing

There were 10 trials that evaluated the effect of temporary pacing on postoperative AF using the standard epicardial

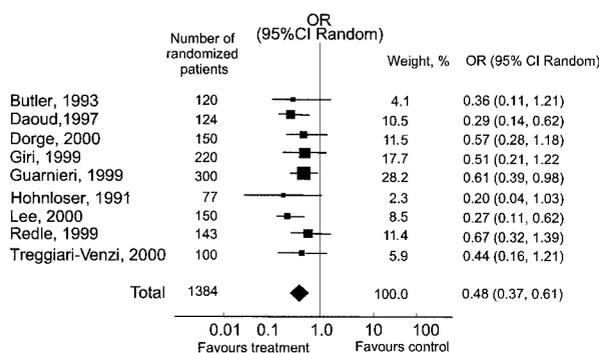


Figure 3. Amiodarone versus placebo or no treatment for the prevention of AF. Test for heterogeneity $P=0.54$. Test for overall effect $P<0.00001$.

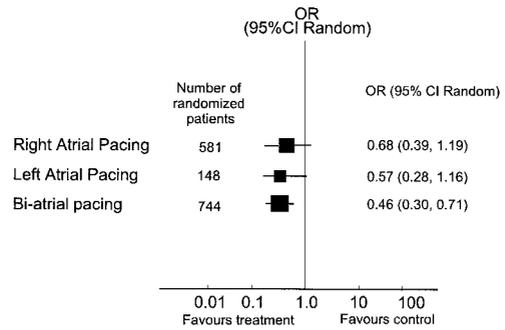


Figure 4. Pacing versus no pacing for the prevention of AF. Test for heterogeneity $P=0.13$.

wires.⁵¹⁻⁶¹ These trials were small, varying in size of treatment groups from 9 to 100 patients. Treatment protocols used different locations of pacing electrodes (right atrial,⁵¹⁻⁵⁷ left atrial,^{54,57} and biatrial pacing.⁵³⁻⁶⁰). Trials also differed in pacing algorithms; some used simple overdrive at a fixed heart rate,^{53,55,59} and others used more complex overdrive algorithms.^{51,54} Patients in the control groups received atrial demand pacing at rates 30 to 45 beats per minute. Pacing from all 3 pacing locations showed a decrease in AF occurrence: biatrial (744 patients enrolled) OR, 0.46 (95% CI, 0.30 to 0.71); right atrial (581 patients enrolled) OR, 0.68 (95% CI, 0.39 to 1.19); and left atrial (148 patients enrolled) OR, 0.57 (95% CI, 0.28 to 1.16) (Figure 4). Both overdriving algorithms showed similar efficacy: OR 0.58 (95% CI, 0.32 to 1.07) for pacing at fixed rates versus OR 0.62 (95% CI, 0.38 to 1.01) for flexible pacing algorithms.

Prevention of Postoperative AF and Length of Hospital Stay

There were 2 β -blocker trials^{13,33} (1200 patients enrolled, 30% of all patients randomized in β -blocker trials) that reported the effect on LOS; β -blockers did not significantly reduce LOS (-0.66 days; 95% CI, -2.04 to 0.72). There were 5 sotalol trials^{9,36,37,39,41} (808 patients enrolled, 62% of all patients randomized in sotalol trials) that reported an effect on LOS data. Sotalol did not significantly shorten of LOS (-0.40 days; 95% CI, -0.87 to 0.08). There were 5 amiodarone trials^{43-46,48} (944 patients enrolled, 68% of all patients randomized in amiodarone trials) that reported the effect on the LOS. Amiodarone reduced LOS significantly by 0.91 days (95% CI, -1.59 to -0.24) (Figure 5).

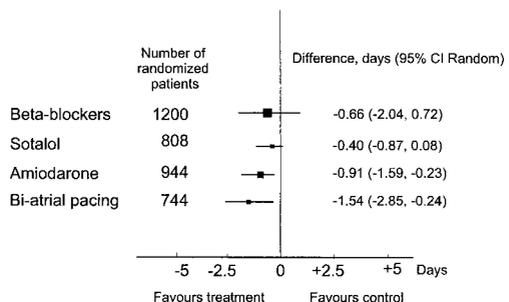


Figure 5. Effect of treatment on hospital LOS.

To obtain the best estimate of the magnitude of the reduction in LOS to be expected from prophylactic pharmacological therapy directed against postoperative AF, the LOS data from all 12 trials with LOS data were pooled (2946 patients). In these 12 trials, drug treatment significantly reduced the percentage of patients with AF from 40% to 25% (OR 0.39; 95% CI, 0.28 to 0.54) and reduced LOS by 0.54 hospital days (95% CI, -0.93 to -0.14). Batrial pacing (744 patients randomized) significantly reduced LOS by 1.54 days (95% CI, -2.85 to -0.24) (Figure 5).

Postoperative AF and Risk of Stroke

To determine if prophylactic treatment to prevent postoperative AF has an effect on postoperative stroke, we obtained all available data regarding this outcome. The incidence of postoperative stroke was available for 14 of 52 trials.^{9,13,28,33,37,41-46,48,54,59} These trials represented data for 2877 of a total of 8122 patients randomized (35%). In these studies, the percentage of patients with AF was reduced from 38.6% in the control group to 23.7% in the treatment group (OR, 0.38; 95% CI, 0.28 to 0.52), which is similar to the overall estimate. The incidence of stroke was 1.2% in treatment group and 1.4% in the control group (OR, 0.90; 95% CI, 0.46 to 1.74).

Discussion

Main Results

Although there have been previous systematic reviews of postcardiac surgery prophylactic therapy against AF, there have been 23 new studies since the last review 12 years ago. The present analysis is important because it is the first to analyze the effects of sotalol, amiodarone, and pacing. It is the first to analyze effect of the interventions on LOS, quantifying clearly the positive effect of AF prevention on this outcome.

Each of the pharmacological interventions evaluated reduces the rate of AF after cardiac surgery. The efficacy of β -blockers, sotalol, and amiodarone seems to be quite similar, although sotalol may be superior to other β -blockers on the basis of small comparative trials. Postoperative pacing is also effective, but the number of patients studied is small, so this conclusion is somewhat tentative. The meta-analysis also demonstrated that pharmacological therapy that reduces AF also reduces hospital LOS by somewhat less than half a day. On the basis of limited available data, there is presently no evidence that prophylactic therapy to reduce AF has an effect on postoperative stroke.

Most patients undergoing CABG or CABG combined with valvular surgery receive a β -blocker preoperatively, and readministration of β -blockers postoperatively is usually easy and safe. β -Blockers clearly reduce postoperative AF. The considerable heterogeneity that we observed in the results in β -blocker trials is unexplained but is not attributable to differences in specific drug used, trial size, or variation in use of preoperative β -blockers. Sotalol and amiodarone are also both effective for the reduction of AF after heart surgery. Although there is some evidence that sotalol is superior to conventional β -blockers, its potential to create proarrhythmic side effects counterbalances possible superior efficacy. Al-

though amiodarone has been shown to be superior to sotalol against chronic AF and is the most widely used antiarrhythmic agent in this setting, its efficacy against postoperative AF is similar to that of β -blockers. Amiodarone is an option in patients with obstructive lung disease, the most common contraindication for β -blockers.

Atrial pacing seems to be effective for prevention of AF after heart surgery. Several variations in pacing site and algorithm have been used with little evidence of superiority of any particular approach. Atrial pacing remains investigational because of limited accumulated experience; however, additional study is warranted.

Hospital Length of Stay

It is generally accepted that one of the main reasons to use prophylactic therapy to prevent AF is to reduce hospital LOS and, in turn, cost of care. This is because postoperative AF is generally of short duration, easy to manage, and relatively asymptomatic. This meta-analysis shows that AF prophylaxis reduces LOS by approximately one half of a day.

The reason the effect on LOS is small, even though the effect against AF is substantial, is easy to understand. The overall effect on LOS is a balance between reduction in AF that decreases LOS and increase in side effects, such as bronchospasm and decreased cardiac output, that tend to increase LOS. Less than half of patients after cardiac surgery will develop any postoperative AF, and still fewer develop prolonged AF, so the effect of drugs on LOS in the patients who are prone to AF has to be very large to be able to detect an effect on LOS in the total population. In addition, all patients receiving treatment are at increased risk of side effects related to the treatment, which can increase LOS. Nevertheless, reduction in LOS of even one half of a day with a simple, inexpensive therapy such as β -blockers can lead to significant cost savings.

Stroke

A relationship between postoperative AF and stroke has been suggested by some authors as another reason for prophylactic therapy to prevent AF.⁶²⁻⁶⁴ Because of the low rate of stroke after heart surgery, no trial of sufficient statistical power can realistically be done. Meta-analysis of available data (limited to 2877 randomized patients) provided no evidence of significant benefit against stroke. The documented point estimate of a 10% decrease of stroke occurrence (with wide confidence intervals) may be an indicator of possible efficacy.

There are also several reasons to surmise that prophylactic therapy against AF will only have a modest effect on stroke. As discussed in relation to LOS, only a fraction of the patients receiving preventive therapy are even theoretically able to benefit, because most patients do not get AF. Postoperative AF may not be the major cause of postoperative stroke, because carotid and aortic disease are involved. Finally, the risk of stroke attributable to postoperative AF is likely very small. If the risk of stroke with postoperative AF is of similar magnitude to the risk of stroke from chronic AF, which is \approx 5% per year, then the risk of stroke during a 1-day episode of postoperative AF would be <1 in 1000.

Limitations

This meta-analysis is limited by the lack of complete availability of relevant data. Stroke rates and length of the hospital stay were not preplanned end points in most included studies. Studies are included that span 3 decades (1979 to 2001), during which time there was intensive evolution of cardiac surgery technique. Nevertheless, treatment benefit seemed to be similar over time.

Practical Considerations

This meta-analysis supports the present recommendation that indicates β -blockers as a first-line medication for prevention of postoperative AF.⁶⁵ Sotalol and amiodarone are also effective and can be considered as appropriate alternatives. A most important measurable clinical benefit, other than AF prevention itself, is reduction in LOS by one half of a day. This could lead to a significant cost savings.

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